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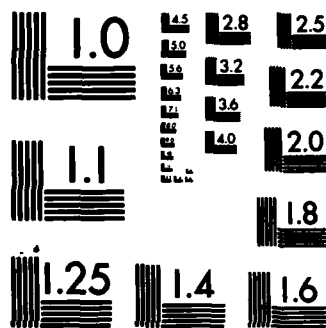
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DEVELOPMENT OF BIODEGRADABLE IMPLANTS  
FOR USE IN MAXILLOFACIAL SURGERY

First Annual Report to

U. S. ARMY INSTITUTE OF DENTAL RESEARCH  
U. S. ARMY MEDICAL RESEARCH AND  
DEVELOPMENT COMMAND

Contract DAMD17-78-C-8059

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**DEVELOPMENT OF BIODEGRADABLE IMPLANTS  
FOR USE IN MAXILLOFACIAL SURGERY**

**ANNUAL REPORT**

**Danny H. Lewis, Richard L. Dunn, Robert A. Casper**

**AUGUST 1979**

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**Southern Research Institute  
Birmingham, Alabama 35205**

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**DEVELOPMENT OF BIODEGRADABLE IMPLANTS  
FOR USE IN MAXILLOFACIAL SURGERY**

**First Annual Report to**

**U. S. ARMY INSTITUTE OF DENTAL RESEARCH  
U. S. ARMY MEDICAL RESEARCH AND  
DEVELOPMENT COMMAND**

**Contract DAMD17-78-C-8059**

**Southern Research Institute  
2000 Ninth Avenue, South  
Birmingham, Alabama 35205  
August 24, 1979**

## I. SUMMARY

This is the First Annual Report on Project 4150, Contract DAMI7-78-C-8509, "Development of Biodegradable Implants for Use in Maxillofacial Surgery". The objective of the project was to develop high-strength resorbable materials useful in the treatment of maxillofacial injuries. To meet this objective, we prepared high-purity monomers, synthesized high-molecular-weight polymers, fabricated the polymers into sample beams, and evaluated the beams for mechanical properties.

Monomers of high purity were prepared by numerous recrystallizations, and their purities were ascertained by differential-scanning calorimetry. These monomers were used to prepare high-molecular-weight polymers of DL-lactide and glycolide. Different levels of chain initiator, optimum reaction conditions, and polymer fractionation were employed to obtain poly(DL-lactide) with molecular weights higher than those previously achieved in our laboratories. Block copolymers of glycolide and DL-lactide were also prepared, but these were insoluble in all common solvents and presented difficulties in characterization and sample fabrication.

The high-molecular-weight polymers were injection-molded into samples for flexural testing. We found, however, that injection molding of the biodegradable polyesters required elaborate precautions to exclude all traces of moisture to prevent a rapid deterioration in molecular weight. The loss in molecular weight with injection molding prevented us from obtaining test samples with the desired high molecular weights and delayed the program several months until we developed an alternate fabrication technique.

Our alternative method which involved several steps gave samples with no significant loss in molecular weight. The polymer was dissolved in a solvent, the polymer solution was cast and dried in a spin cup to yield a film, the film was cut into sections, and the sections were laminated under heat and pressure to form samples suitable for testing. The solvent and the polymer molecular weight both affected the mechanical properties of the laminate. Poorer solvents gave laminates with better mechanical properties, and higher-molecular-weight polymers gave more flexible laminates.

The lamination technique developed to prevent a loss in molecular weight with sample fabrication was easily adapted to the addition of reinforcing materials to the polylactide films. Polyglycolide fibers and carbon fabric were incorporated into laminates of poly(DL-lactide). The polyglycolide fibers were melt-spun from high-molecular-weight polymer prepared in our laboratory. The fibers were knitted into tubing and coated

with polylactide, but the resultant structure was too flexible for lamination. Polyglycolide sutures were formed into a continuous web, the web was coated with polylactide, and the fiber film was laminated with other films of poly(DL-lactide). The laminated sample had a low flexural modulus. The suture fibers with their high elongation value of 15% tended to stretch when the composite materials were flexed, and thus did not provide a reinforcing effect. However, the low elongation and high modulus of the carbon fibers provided the stiffness and rigidity required for high flexural properties. Their incorporation into polylactide laminates gave flexural strength and modulus values equivalent to those of bone.

Another successful approach to attainment of high-strength materials was polymer orientation. Laminates of poly(DL-lactide) were oriented by stretching them at the glass-transition temperature. The oriented polymer samples gave modulus values four times those of control samples.

Of the many approaches to high-strength resorbable implant materials proposed and studied, only the lamination technique with incorporation of reinforcing fibers and the orientation of samples provided materials with significant improvements in flexural properties. After further research and optimization studies, these approaches should lead to satisfactory biodegradable materials for in vivo evaluations by the Army.

## II. INTRODUCTION

The need for improved methods and materials for the management of severe maxillofacial wounds is well recognized in view of the substantial portion of these in recent conflicts. In its investigations of various approaches to improved surgical methods and patient care, the Army Institute of Dental Research has constantly sought better materials for repair of jaw fractures.

Bone consists of a framework of collagenous fibers, a mineral matrix, which is primarily calcium hydroxyapatite, and a small amount of polysaccharides. Even though a large portion of the volume of bone is water, bones are hard and tough. Although varying considerably in properties depending on function, bones commonly have tensile strengths of 6,000 to 20,000 psi and values of modulus of elasticity of 1 to  $3 \times 10^6$  psi. Metals are stronger and stiffer than bone. Most polymeric materials are as strong as bone but more deformable, and require fiber reinforcement to equal the stiffness characteristic of bone.

Historically, metals have received wide applications as bone plates and other fracture fixation devices. Metals exhibit high values of tensile strength and compressive moduli, they can be fabricated into fixation hardware by conventional techniques,



and they usually provide excellent resistance to a variety of environments including sterilization and implantation. However, because of their high strength and stiffness, metals absorb essentially all the load and stress applied to the fractured bone. This condition is desirable in the initial stages of healing to prevent movement and promote primary osseous union, but undesirable later, when stress must be applied to the bone to prevent resorption and atrophy. This protection from stress by metals results in a mechanically inferior bony structure in the region of the plate, and refracture is likely upon removal of the metal.

The removal of the metal fixation device requires follow-up surgery, another disadvantage. As demonstrated by the Army Institute of Dental Research, this problem can be alleviated through the use of biodegradable polymers as resorbable plates. Aliphatic polyesters such as polylactide and polyglycolide were fabricated in the shape and to the approximate dimensions of conventionally used steel plates. Screws of these polymers were used to fix the plates to the mandibles of dogs. The animals were sacrificed at intervals up to 40 weeks, and no signs of rejection, edema, or discoloration were observed. After 40 weeks, neither the fracture site nor any evidence of an increase of collagen formation or scar tissue could be found. Those experiments demonstrated that mandibular fixation with resorbable implants is possible, that the devices can be customized, and that degradation is slow and uneventful. The aliphatic polyesters are completely resorbed in the body; surgery for their removal is thus not required.

Although the results of these pilot studies demonstrated the potential of biodegradable polymers in oral surgery, the experiments also revealed deficiencies with the implants. Primarily, the implants used in the preliminary studies did not exhibit sufficient flexural rigidity during the first four to six weeks post implantation. Most of the implants used by the Army exhibited flexural strengths of 10,000 to 20,000 psi and flexural modulus values of  $0.5$  to  $1 \times 10^6$  psi. These modulus values are lower than those of bone, and as expected, the materials bend and deform to a greater extent. A higher axial modulus and bending rigidity are needed in the biodegradable materials if they are to be used successfully for implantation.

The sections which follow describe the research carried out on Contract DAMI7-78-C-8509 from August 1, 1978, to July 31, 1979.

### III. POLYMER PREPARATION

Several approaches exist for the improvement of the mechanical properties of the thermoplastic polyesters. Both chemical and physcial methods have proven useful for other polymer systems. In

the numerous technical publications and patents which deal with improvement in the moduli and flexural strengths of thermoplastics, polymer molecular weight is the most common variable. Often, the flexural strength can be increased as much as ten fold by increasing the molecular weight of the polymer. For this reason, we prepared high-molecular-weight biodegradable homopolymers and copolymers from ultrapure monomers with different initiator levels and reaction conditions. We also fractionally precipitated high-molecular-weight polymer to obtain even higher-molecular-weight material.

#### A. Monomer Preparation

The first and perhaps most crucial step in any polymer development program directed toward improving properties is the preparation of high-purity monomers. This is especially true for biodegradable polymers of lactic and glycolic acids.

The DL-lactide, as received from Clinton Corn Processing Company of Clinton, Iowa, is impure; its melting point is usually  $<113^{\circ}\text{C}$ . To 6.0 kg of crude DL-lactide was added 12 liters of isopropanol, and the mixture was heated to the boiling point until all the lactide dissolved. Heating was discontinued, and the mixture was allowed to cool slowly to room temperature. The mixture was cooled to  $5^{\circ}\text{C}$ , and the crystallized lactide was isolated by inverted filtration. In the next recrystallization, one part of lactide was added to six parts of benzene, and 3.0 g of activated charcoal was added. The mixture was heated to reflux and filtered while hot through a sintered-glass funnel containing a bed of glass wool. The mixture was then heated to the boiling point again, and two parts benzene were removed by distillation to azeotrope out residual water. The solution was allowed to cool to room temperature. The crystalline lactide was isolated by filtration and protected from atmospheric moisture with a rubber dam during the filtration. The recrystallization from benzene was repeated twice more, without charcoal, and the lactide was dried in a vacuum oven at  $50^{\circ}\text{C}$ . The total recovery of purified lactide was 2.6 kg, and the monomer had a melting point of  $126\text{--}127.5^{\circ}\text{C}$ .

The glycolide monomer was prepared and purified by the following method. In a three-neck flask equipped with a thermometer, a distillation head, and a condenser was added 6 kg of a 65% aqueous solution of glycolic acid (Ashland Chemicals). The mixture was heated to boiling, and the water was distilled off. When the water ceased to distill, the system was placed under a water-aspirator vacuum, and the mixture was maintained below  $180^{\circ}\text{C}$  until the reaction water was completely removed. The resulting molten low-molecular-weight polyglycolide was slowly poured into a stirred isopropanol at  $5^{\circ}\text{C}$ , and the prilled material was collected as a light brown solid on a Buchner funnel. The polymer was dried in a vacuum oven at room temperature for 24 hours.

The low-molecular-weight polyglycolide was separated into smaller portions and thermally cracked to form glycolide. To 1 kg of polymer in a three-neck flask, connected to two additional flasks utilized as receivers for the glycolide, was added 10 g of antimony (III) oxide catalyst. The pressure of the system was reduced to about 3 mm, and the temperature was raised to about 270°C over 8 hours. The crude glycolide distilled as it formed and was collected as a solid in the traps, which were cooled with dry ice and acetone. The light yellow distillate was melted and poured slowly into isopropanol at 5°C, and the prilled glycolide was collected by filtration and protected from atmospheric moisture with a rubber dam during isolation. The yield of glycolide was 920 g (92%).

Several portions of prilled glycolide were combined and recrystallized twice from dry ethyl acetate. The purified monomer was dried in vacuo in a desiccator heated to 60°C. The melting point of the purified glycolide was 79-80.5°C.

## B. Polymer Synthesis

Various molecular weight polymers of DL-lactide were prepared with different amounts of lauryl alcohol as the chain initiator. Polyglycolide for later use in fiber spinning, and block copolymers of lactic and glycolic acids, were also prepared.

### 1. Poly(DL-lactide) (PLA)

One approach to achieving a high-molecular-weight polymer from cyclic monomers is the use of a chain initiator in the polymerization to start the growth of just a few polymer chains. The resulting polymer should comprise relatively long chains, and the number of chains will correspond to the number of molecules of initiator. Lauryl alcohol is often used as the initiator in polylactide polymerizations. However, it can also serve as a chain terminator since it is monofunctional. In order to determine the effect of initiator concentration upon the degree of polymerization, we prepared three batches of polylactide with different amounts of lauryl alcohol. A typical synthesis is described below:

To a dry, 2000-ml, three-neck flask, equipped with a mechanical stirrer and a nitrogen inlet, were added 1500 g of DL-lactide, 15 drops (0.04%) of lauryl alcohol, and 0.3 g (0.02%) of tetraphenyltin. The loading of the reaction vessel was carried out in a nitrogen-filled dry box. The flask was removed from the dry box, connected to a nitrogen line, placed in a oil bath preheated to 170°C, and stirred for 3 hours. Stirring was discontinued, but heating was continued for an additional 18 hours. The polymer was allowed to cool to room temperature, and then

it was frozen in a dry-ice bath. The flask was broken, and the frozen polymer was removed and dissolved in methylene chloride. The viscous solution was poured slowly into stirred methanol, and the precipitated polymer was collected and dried in vacuo at 50°C.

Since the growing polymer chains can be terminated prematurely by reaction with available hydroxyl groups on the surface of the glassware, we coated all the glassware with Surfasil™, a silicon material which forms a chemically-bonded, inert film on the surface of the glass. The results of these three polymerizations are given in Table I.

Table I. Effect of Lauryl Alcohol Concentration on Molecular Weight

Batch 9052-	Lauryl Alcohol, weight %	Inherent Viscosity, dl/g
51	0.00	1.35
52	0.02	1.34
34	0.04	1.27

The data indicate that the outcome of the polymerization is not completely controlled by the amount of lauryl alcohol added. Theoretically, the viscosity of the polymer should increase as the amount of lauryl alcohol is reduced. However, it appears that a limiting viscosity has been reached. This limit to the molecular weight may be imposed on the polymer by the purity of the monomer, although the monomers in these polymerizations were recrystallized to greater than 99.4% purity. It is possible that the stereo-irregularity of the DL-lactide prohibits high viscosity polymer since polymers of stereoregular L-lactide with inherent viscosities of 7.0 dl/g have been obtained by other investigators.

## 2. Polyglycolide (PGA)

A batch of medium-molecular-weight polyglycolide for use in synthesis of block copolymers and for spinning of fibers for reinforcements was prepared by the following procedure:

Purified glycolide monomer was placed in a flask and distilled into a flask for polymerization. The polymerization flask was equipped with a mechanical stirrer and a gas adapter. Antimony trifluoride, 0.03% by weight, was added as a catalyst. The reaction vessel was connected to a nitrogen line and placed in an oil bath at 170°C. Stirring was begun when all the glycolide had melted. The reaction was stirred for 2 hours and 40 minutes at which time it became too viscous

to stir. Heating was continued for another 6 hours and then the polymer was allowed to cool slowly for 16 hours. The reaction flask was broken away, and the polymer was ground in a Wiley Mill. The ground polymer was demonomerized by heating it at 130°C under vacuum for 132 hours. The inherent viscosity of the resulting polymer as measured in hexafluoroacetone sesquihydrate at 30°C was 1.27 dl/g.

### 3. Block Copolymers

In a variety of industrial applications, block copolyesters have been obtained by the end-to-end linking of polyester oligomers and other polymers. The resulting polymers show distinct advantages in physical properties, particularly higher values of modulus. For this reason, we investigated the synthesis of block copolymers of lactic and glycolic acids. Both materials are biodegradable, but the polyglycolide is more crystalline than poly(DL-lactide) and should exhibit higher modulus values. For our first block copolymer, we prepared low-molecular-weight polylactide by degrading medium-molecular-weight polylactide. Portions of the higher-molecular-weight polymer were steam autoclaved to produce samples of lower molecular weight. In our initial experiments, we steam autoclaved 1-g samples of PLA at 120°C and 15 psig for varying times. Figure 1 shows the correlation between inherent viscosity and time. From this plot we selected the appropriate time to autoclave larger amounts of PLA. The larger samples (200 g) was steam autoclaved and then dissolved in p-dioxane, precipitated into deionized water, and dried under vacuum. The inherent viscosity of the polymer before autoclaving was 0.59 dl/g, and after 60 minutes in the autoclave, it was 0.21 dl/g. Approximately 75 g of the low-molecular-weight PLA was placed in a three-neck flask which was cooled in dry ice and acetone, and 25 g of purified glycolide was distilled in (under high vacuum). The flask was allowed to reach room temperature, and then 2 mg (0.02%) of tetraphenyltin was added. The flask was connected to a nitrogen line and heated to 170°C in an oil bath for 4 hours. The polymer was then cooled and isolated. Viscosity measurements showed it to be low-molecular-weight material.

A second attempt to prepare block copolymers utilized a different catalyst system. In a three-neck, round-bottom flask equipped with a mechanical stirrer, a nitrogen inlet, and a rubber septum was placed 11.0 g of DL-lactide. The flask was warmed to 120°C and 50  $\mu$ l of a 25% solution of diethyl zinc in hexane was added. No reaction was observed so an additional 50  $\mu$ l of catalyst solution was added. Finally, after another 50  $\mu$ l-aliquot of catalyst was added, the viscosity increased greatly. After a period of 5 minutes, 4.0 g of glycolide was added, and the mixture was allowed to stir for 30 minutes until the high viscosity of the polymerizate prevented further stirring. When the polymerizate was cooled, two layers appeared in the flask.

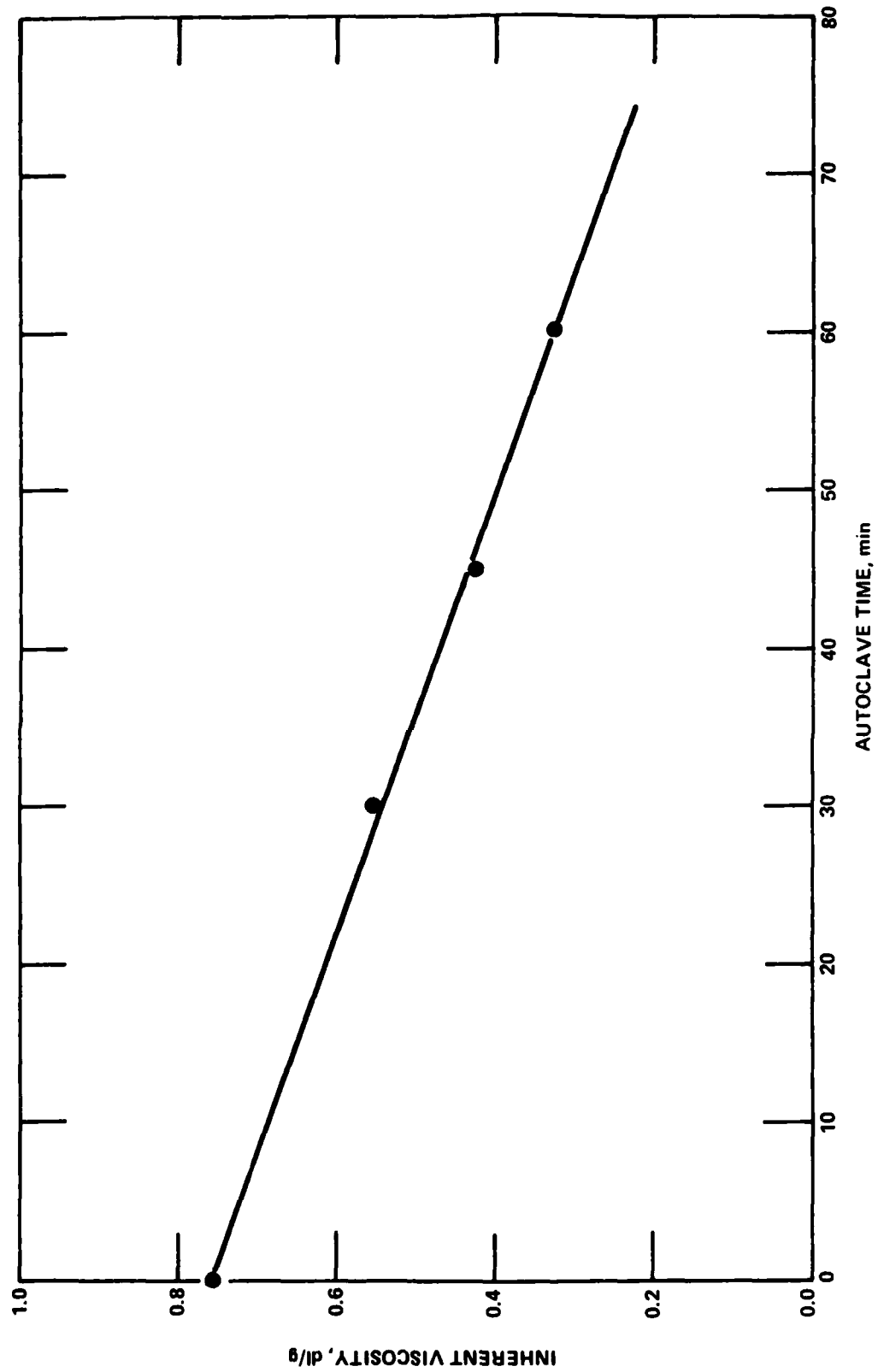


Figure 1. Inherent Viscosity of PLA as a Function of Time in Autoclave.

The upper layer was white and believed to be a homopolymer of glycolide. The lower layer was pink and thought to be polylactide. Addition of methylene chloride gave a soluble fraction having an inherent viscosity of 1.09 dl/g. The remaining fraction was broken away from the flask and dried. The product which was insoluble in common organic solvents was not characterized further.

A third attempt to prepare a suitable block copolymer involved sequential addition of the monomers in four stages. The polymerization was initiated by the addition of 50  $\mu$ l of the diethyl zinc solution to 11.0 g of DL-lactide at 125°C. The viscosity began to build after 2 minutes and then 4.0 g of glycolide was added. After 2 more minutes an additional 11.0-g charge of DL-lactide was added. After 2 more minutes, a final 4.0-g charge of glycolide was added. The mixture was heated with stirring for 2 hours. Upon cooling 3 separate layers of polymer were observed in the flask. These products which were insoluble in common organic solvents were not characterized.

We also attempted to prepare a 75/25 lactide/glycolide block copolymer by a transesterification in the melt of the two homopolymers using para-toluenesulfonic acid as a catalyst. Difficulties were encountered because of the large difference in the melting points of the two homopolymers. Polylactide melts at about 170°C, and prolonged heating at the temperature required to melt polyglycolide (230°C) promotes the decomposition of polylactide.

None of the procedures that we employed gave block copolymers with properties suitable for sample molding. Considerable research and effort will be required to develop methods for the preparation of block copolymers of lactic and glycolic acids to be used in biodegradable implants.

### C. Polymer Fractionation

The biodegradable polyesters are polydisperse materials with wide molecular-weight ranges. Thus, the polymers contain high-molecular-weight material mixed with a significant portion of low-molecular-weight oligomers. Separation of the high-molecular-weight portion from the oligomers should give polymers with higher molecular weights than normally obtained in polymerization. We developed a technique for the fractional precipitation of PLA and employed it to fractionate 70 g of PLA with an inherent viscosity of 1.33 dl/g. In our procedure, a 7-percent solution of polylactide in dioxane was prepared in a 4-liter vessel equipped with a drain at the bottom. The solution was stirred as isopropanol, a nonsolvent for PLA, was added dropwise. When a slight turbidity developed in the solution, the addition of the nonsolvent was stopped. The solution was warmed until it became homogenous, and then it was allowed to cool slowly to ambient temperature. The precipitated phase

was allowed to settle, and then it was drained from the bottom of the flask. The fractionated polymer was further purified by dissolution in dioxane and precipitation into water. The polymer fractions were dried in vacuo. The results obtained are given in Table II.

Table II. Fractionation of Polylactide

<u>Polymer Fraction</u>	<u>IPA Added, ml</u>	<u>Polymer Wt, g</u>	<u>Polymer Recovery, %</u>	<u>Inherent Viscosity, dl/g</u>
1	1300	44.27	63.2	1.60
2	165	10.24	14.6	1.16
3	140	--	--	--

Since we were primarily interested in the highest molecular-weight fraction, we did not carry out the fractionation to 100% recovery. The polymer with an inherent viscosity of 1.60 dl/g is the highest-molecular-weight PLA that we have obtained in our laboratories.

#### D. Polymer Characterization

All the polymers that we prepared for fabrication into test samples were characterized by inherent viscosity measurements and differential-scanning calorimetry. We also developed a procedure for determining the number of carboxylic acid endgroups in PLA. Essentially, the procedure consists of dissolving the polymer in chloroform and titrating to a phenol red endpoint with 0.1 N sodium hydroxide in benzyl alcohol. Our initial results indicate, as expected, that the number of titratable endgroups varies inversely with the polymer molecular weight (inherent viscosity). As Figure 2 indicates, a linear relationship exists between the inherent viscosity and the number of carboxylic acid endgroups (equivalent COOH/ $10^6$  gm). In addition, we found that as much as 0.5% of lactic acid (or its equivalent) is removed from the polymer when it is precipitated from dioxane into water.

#### IV. PREPARATION OF POLYGLYCOLIDE FIBERS

Fibers of polyglycolide were prepared by melt spinning the resin with a ram extruder at 235°C. Some of these fibers were drawn (oriented) and knitted into a "sock", a tubular knit, which was later laminated with polylactide films as a reinforcement.



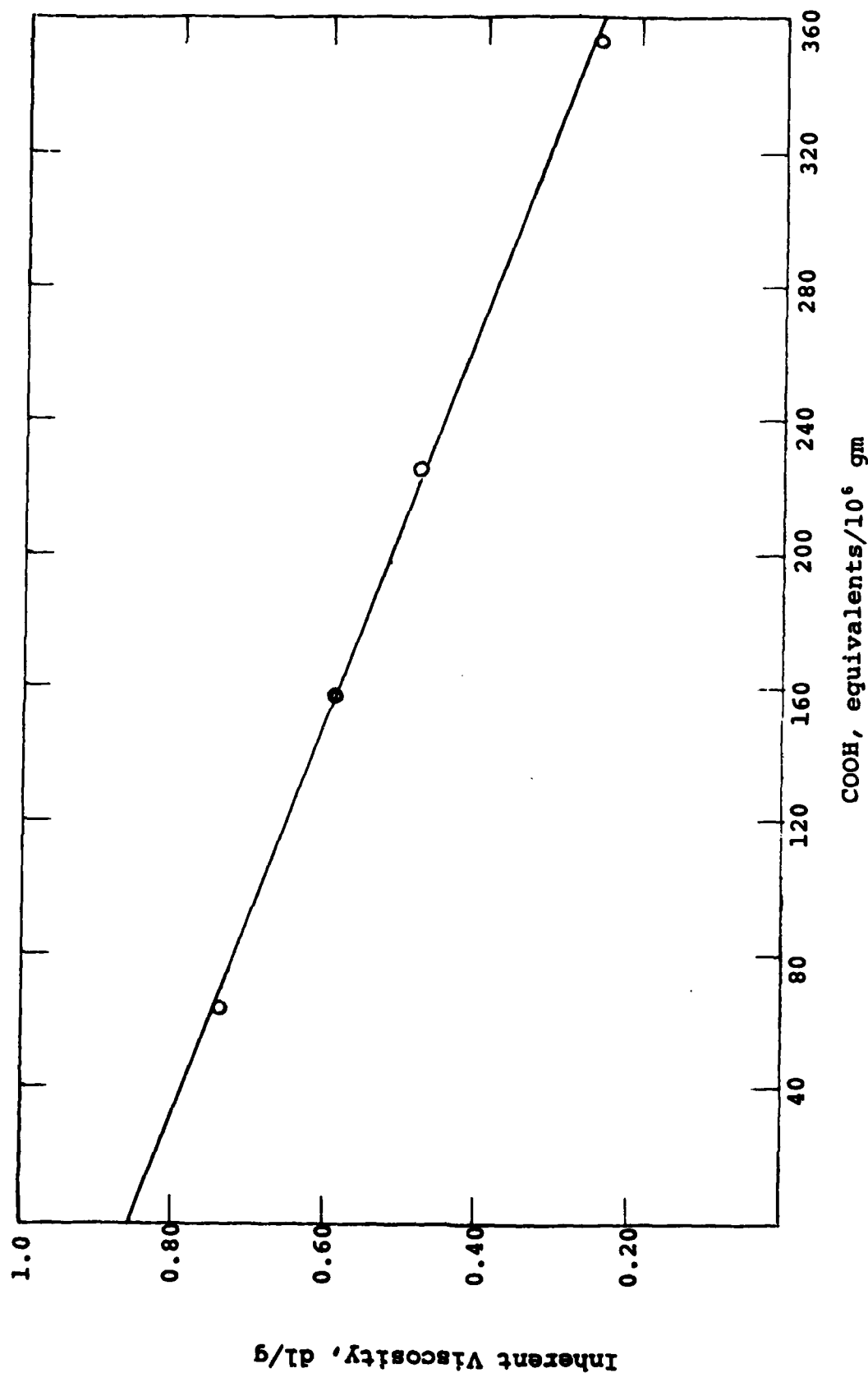


Figure 2. Plot of the Equivalents of Carboxy Endgroups versus the Inherent Viscosity of DL-PLA

## V. FABRICATION OF SAMPLES

The poly(DL-lactide) materials were fabricated into samples 3 inches long, 0.5 inch in width, and 0.125 inch in depth for flexural testing. In the initial fabrications we used melt-injection equipment, but we later changed to lamination of cast films due to polymer degradation during injection-molding.

### A. Injection Molding

Two samples of PLA were dried under vacuum for 16 hours. A Frohring Mini-Jector, Model-45 injection-molding apparatus was used to prepare beams from the samples. The low-molecular-weight sample, which had an inherent viscosity of 0.45 dl/g, was injection-molded at 135°C. The high-molecular-weight sample, inherent viscosity 1.30 dl/g, required a temperature of 255°C for successful molding. All samples were conditioned before testing by storing them in a desiccator over Drierite for 24 hours in a room maintained at 72°F and 63-65% relative humidity. When we examined small pieces of PLA taken from the surface of an injection-molded sample, we found that serious degradation had occurred. The inherent viscosity had fallen from 1.27 to 0.7 dl/g. Apparently, the fabrication process with prolonged exposure to heat, moisture, and oxygen degraded the polymer.

### B. Lamination

Since our injection-molding apparatus did not allow us to exclude air, we investigated an alternate method of fabrication. Thin films of polylactide (inherent viscosity of 1.25 dl/g) were prepared by a spin-casting technique. A dilute solution of the polymer in 1,1,1-trichloroethane was added to a teflon-coated cup which was rotating at 3500 rpm. When the solvent had evaporated, the film was removed and dried in vacuo at 60°C for 5 to 7 days. This procedure was repeated several times to obtain enough films to prepare laminates 0.125 inch in thickness for flexural strength tests. The films were cut into pieces 2.5 inches by 0.5 inch. Approximately ten films were laminated together for 1 hour in a press heated to 80°C to afford a sample 0.125 inch thick. The laminates were removed and trimmed to the desired width of 0.5 inch since some spreading had occurred under pressure. The laminate appeared to be a homogeneous structure when viewed in cross section. Similar films were prepared with dioxane as the casting solvent. This method of sample preparation gave us a very small drop in viscosity compared to injection-molding. With 1,1,1-trichloroethane the viscosity of a laminated sample was 1.19 dl/g compared to the initial value of 1.25 dl/g; with dioxane the viscosity was 1.28 dl/g compared to the initial value of 1.33 dl/g. The spin-casting technique also gave us films suitable for incorporation of reinforcing fibers.

## VI. PREPARATION OF FIBER-REINFORCED MATERIALS

Incorporation of reinforcing fibers in polymeric materials has proven to be a useful procedure for improving their mechanical strength. Short fibers of glass, carbon, and synthetic polymers have been incorporated within polymer matrices as inert fillers, and woven fabrics have been impregnated and laminated with plastic and elastomeric films. These approaches offer advantages in improvement of mechanical strength. In our studies, we investigated the effects of polyglycolide and carbon fibers upon the flexural properties of PLA samples.

### A. Biodegradable Fiber Reinforcement

The best fiber reinforcement for a biodegradable polymeric implant would also be biodegradable; thus, we examined the use of an absorbable fiber system. The knitted tubular sock of polyglycolide fibers described earlier was stretched tightly over two posts and then painted with several coats of a solution of PLA in methylene chloride until the knitted fabric was completely encapsulated in the polymer. The fabric-reinforced film was then cut free of the posts and dried in vacuo. The resulting film was far more flexible than a film of PLA alone. Apparently the knit possessed the ability to bend and stretch still further. We did not prepare any laminates from this film due to its high extensibility which would give no reinforcement.

Since the knitted tubing was too flexible for reinforcement, we decided to examine absorbable sutures. Dexon sutures, consisting of high-strength braided polyglycolide fibers, were obtained commercially in thirty-inch lengths. The sutures were tied together to produce one continuous braid, and then wrapped around two posts which were 3 inches apart. The resulting structure contained two separate layers of fibers measuring 3 inches by 3 inches. Each layer of fibers was painted with several coats of solution of PLA in methylene chloride until they were encapsulated in the polymer. The film was then cut free of the posts and dried in vacuo. These films were firm and were used in subsequent lamination of PLA material.

### B. Carbon Fiber Reinforcement

Carbon fibers are not biodegradable; however, they have been shown to be bicompatible, posing no threat to the body if they are unable to migrate from the implantation site. Other investigations have shown that carbon fibers are encapsulated by the regenerating bone as healing proceeds. Since high-modulus carbon fibers are well known for their ability to improve mechanical properties, such as flexural strength and modulus in other composite materials, we investigated their ability to improve our system. The procedure was quite simple.

A square-weave fabric of carbon fibers made by carbonization of woven rayon yarns was obtained from Union Carbide Corporation. A sheet was cut from the woven sample which had the same measurements as our spin-casting cup. Approximately 30 grams of a 13% solution of polylactide (inherent viscosity 1.33 dl/g) in dioxane was added to the teflon-coated cup rotating at 3500 rpm. When most of the solvent had evaporated, the sheet of carbon fibers was placed in the spin cup. An additional 40 grams of PLA solution was added to the rotating cup which was allowed to spin until the film appeared to be free of solvent. The resulting film completely encapsulated the carbon fibers and filled the holes within the weave. However, the film still contained traces of solvent since it was soft and flexible. It was dried at 60°C in vacuo until it was stiff and hard. It was then used in laminates with PLA films.

The size of the specimens required for ASTM Test D790 for flexural strength is a beam 0.125 inch thick, 0.5 inch wide, and a minimum of 2.5 inches long. The thin films described above were cut into segments 3 inches by 0.5 inch and laminated in a heated press to produce a sample of the desired 0.125 inch in thickness. Control samples of the PLA films and laminates containing carbon fibers were prepared at 80°C. Films which contained sutures of polyglycolide fibers were pressed together at 45°C. The reduced temperature was required in order to remain below the glass transition temperature of the polyglycolide fibers, about 60°C. At this temperature the fibers would undergo a phase transition which would allow them to relax and thereby lose the strength that was gained from the drawing process. Laminates containing suture fibers were prepared with the fibers running in the longitudinal direction (along the 3-inch length of the sample) such that the fibers would be broken by the flexural strength test.

## VII. POLYMER ANNEALING

Often plastics are annealed to yield high-strength materials. The temperature and duration of the annealing process is usually dictated by the glass transition temperature and thermal stability of the specific polymer. To improve the flexural strength of injection-molded PLA samples, we studied the effect of annealing on their mechanical properties. Annealing a sample for several hours at a temperature close to the glass-transition temperature allows the polymer segments to realign themselves in an orderly fashion. If stresses were "frozen in" the sample when it was injection molded, annealing the sample will remove these stresses and increase the material's resistance to fracture. In a preliminary

experiment, we annealed a sample of injection-molded PLA at 55°C for 5 hours in a silicone oil bath. The temperature was then reduced slowly to ambient temperatures over a period of several hours. The resulting sample did not have improved physical properties. Apparently, the injection-molded samples of amorphous PLA do not benefit from annealing.

#### VIII. POLYMER ORIENTATION

In the production of synthetic sutures, the melt-spun fibers are rarely strong enough to be useful when they are first spun. However, if the fibers are drawn about 6X in the presence of heat, the mechanical properties increase dramatically. The drawing process aligns the polymer chains and affords a high degree of orientation. Almost all synthetic fibers are treated in a similar fashion, but the process is not as widely used for other plastics of different geometry.

A thick slab of PLA was prepared by lamination of enough films to make a sample 1 inch by 0.25 inch by 3 inches. This sample was oriented by our drawing it to two times its original length in an Instron equipped with a heating chamber adjusted to 60°C. The polymer was drawn at the rate of 2 inches per minute. Problems were encountered with the sample "necking" and slipping out of the clamps. However, a sample was obtained suitable for testing.

A similar orientation trial with a thick slab of polycaprolactone failed because of the low melting point of the polymer. The heat required for orientation caused the polymer to melt and the sample to slip in the clamps. However, the orientation of a laminate of PLA with Dexon sutures was more successful. The composite structure was drawn 1.2X to give a firm, rigid sample.

#### IX. SAMPLE EVALUATIONS

The samples prepared by injection-molding and lamination of films with and without fiber reinforcement were tested for flexural properties. The polymer samples that were annealed or oriented were also evaluated.

##### A. Determination of Flexural Properties

The determination of flexural strength was carried out in accordance with ASTM Procedure D790 "Flexural Properties of Plastics" - Method I. This test is designed for rigid or semi-rigid materials that break or rupture before a maximum strain of 5% is reached in the outer surface of the samples. A three-point loading system utilizing center loading

on a beam resting on two supports set 2 inches apart was affixed to an Instron Tensile Testing Machine, Model TM-S. The samples were subjected to an increasing load at a rate of 0.02 inch per minute. All samples were at least 3 inches long and 0.5 x 0.125 inch in width and depth. The flexural strength,  $S$ , and the tangent modulus of elasticity,  $E_B$ , were calculated according to the following equations:

$$S = 3PL/2bd^2$$

$$\text{and: } E_B = L^3m/4bd^3$$

where:  $S$  = stress in the outer surfaces at midspan, psi

$P$  = load at a given point on the load-deflection curve, lb.

$L$  = support span, in.

$b$  = width of beam, in.

$d$  = depth of beam, in.

$E_B$  = modulus of elasticity in bending, psi

$m$  = slope of the tangent to the initial straight-line portion of the load-deflection curve, lb/in. of deflection

Our procedures for testing the polymers were identical to those used by other investigators who have previously supplied the U. S. Army Institute of Dental Research with polymer specimens. The results should be directly comparable.

#### B. Results of Flexural Tests

The poly(DL-lactide) samples prepared by injection-molding of polymers with low and high molecular weights demonstrated the effects of molecular weight upon flexural properties. Although the values are different, the same relationship is illustrated by flexural tests on PLA laminates prepared from films spun-cast from dioxane. These results given in Table III show that higher-molecular-weights do not improve the flexural properties of PLA polymers. In fact, the higher-molecular-weight polymers gave laminates with lower flexural properties than those of the low-molecular-weight materials. Since we used amorphous poly(DL-lactide) in our laminates, the only resistance to bending was derived from intramolecular and intermolecular forces with no crystallinity effects. The longer polymer chains in the high-molecular-weight materials with their interchain entanglements allow the material to bend and flex more before breakage. Thus, higher molecular weights in amorphous polymers may give tougher materials with

Table III. Effect of Molecular Weight on Flexural Properties of PLA

Fabrication Method	Inherent Viscosity, dl/g	Flexural Strength $\times 10^3$ psi	Modulus of Elasticity $\times 10^6$ psi
Melt-injection	0.45	6.9	1.73
Melt-injection	1.30	10.5	0.48
Spin-casting	1.33	5.8	0.27
Spin-casting	1.60	2.8	0.14

the ability to flex and absorb impact, but they do not improve the rigidity and resistance to bending forces.

In our lamination process, we detected differences in flexural properties of PLA films cast from different solvents. Films cast from poorer solvents gave laminates with better mechanical properties as shown in Table IV. Dioxane is a better solvent for PLA than 1,1,1-trichloroethane since the inherent viscosity of the PLA material in dioxane was 1.28 dl/g compared to a value of 0.88 dl/g in 1,1,1-trichloroethane. Apparently the poorer solvation diminished the extent of coiling and interchain entanglement with a resultant increase in density and modulus.

Fiber reinforcement of PLA samples gave the most significant improvement in flexural properties. As shown in Table V, the addition of 11% of carbon fabric in the form of one layer of carbon weave in the center of the laminate had little effect on the modulus, but it did improve the flexural strength. The modulus was similar to the control sample because a beam under a three-point load experiences the most stress on the outside faces where it is being compressed or stretched to the greatest degree. Theoretically, the middle of the beam experiences no stress; so as expected, placement of the carbon weave in the center did not improve the modulus. However, the flexural strength of this sample was increased because of the higher tensile strength of the carbon fibers which were broken in the test. The addition of 55% of carbon fabric in the form of alternating layers of carbon weave films and PLA films resulted in dramatic increases in both the flexural strength and the tangent modulus of elasticity. The flexural strength value represents a 460% improvement over the control; while the modulus value shows an improvement of 690%. In this sample, the reinforcing carbon fibers were located at points of high stress and thus gave the expected improvement in properties. Even better improvements would be obtained if all the high-modulus carbon fibers were laid in the longitudinal direction; however, the reinforcement in strength would be only unidirectional. The woven carbon fabric which is easily added to the PLA material provides reinforcement in two directions and should give a better overall implant material. The results obtained with carbon-fiber reinforcement definitely show promise as a means of providing a suitable implant material.

The results obtained with the Dexon sutures were not as encouraging as those obtained with the carbon fibers. Two factors may have contributed to the lack of reinforcement. First, it is difficult to wind the sutures tightly around the posts and not have any loose ends in the matrix. Second, the braided sutures by the nature of their fabrication will extend to some length before they become taut. At this point, the fibers in the braid will start to elongate before they reach their breaking point. Since the fibers have an elongation of 15%, they never reached



Table IV. Effect of Solvent on Mechanical Properties of Poly(DL-lactide)

<u>Inherent Viscosity, dl/g</u> <u>Initial</u>	<u>Final</u>	<u>Casting Solvent</u>	<u>Flexural Strength</u> <u>X 10<sup>3</sup> psi</u>	<u>Flexural Modulus</u> <u>X 10<sup>6</sup> psi</u>
1.33	1.28	Dioxane	5.8	0.27
1.33	--	TCE <sup>a</sup>	7.1	0.31
1.30	0.76	Melt	10.5	0.48

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<sup>a</sup> TCE = 1,1,1-trichloroethane

Table V. Fiber Reinforcement of Poly(DL-lactide)

<u>Sample</u>	<u>Flexural Strength</u> <u>X 10<sup>3</sup> psi</u>	<u>Flexural Modulus</u> <u>X 10<sup>6</sup> psi</u>
PLA Control	5.8	0.27
PLA + 11% Carbon	7.5	0.27
PLA + 55% Carbon	27.0	1.83
PLA + 50% PGA sutures	2.3	0.09
PLA + 50% PGA sutures oriented	4.1	0.20

the breaking point in the flexural test and thus contributed little to reinforcement. In fact, the test specimens containing the Dexon sutures did not break, they simply yielded. To obtain reinforcement with the sutures, it will be necessary to remove all the extension or elongation in the fibers. We tried to accomplish this task by drawing a sample beam of sutures laminated with PLA films. We only drew the beam 1.2X in order to remove the elongation from the fibers. As expected, we did obtain some improvement in flexural properties, but the values are considerably lower than those achieved with carbon reinforcement.

Orientation of the PLA samples by hot drawing increases the modulus of elasticity as shown in Table VI. We obtained with the oriented sample an increase of 400% over the control sample even though the flexural strength was not affected. Apparently, when the sample is originally cast, some polymer chains are positioned in relatively straight lines; however, most of them are coiled and twisted. In breaking the control sample, little resistance is encountered to bending under the three-point load because the strain is absorbed by the chains as they straighten out. The flexural strength provides a measurement of the force required to break a straightened chain. Orientation of the samples "pre-straightens" the chains. There is high resistance to any further bending, and therefore, a high modulus is obtained. However, the flexural strength is similar because it is still related to the strength of a PLA chain.

#### X. CONCLUSIONS AND RECOMMENDATIONS

Work completed on Contract DAMD17-78-C-8059, "Development of Biodegradable Implants for Use in Maxillofacial Surgery" has identified both potentially successful approaches in developing high-strength resorbable implant materials and less promising methods.

Poly lactide, like other polyesters, is susceptible to hydrolysis in the presence of moisture and heat. We found that injection molding of poly lactide without elaborate precautions to exclude all traces of moisture leads to rapid deterioration in molecular weight with a subsequent loss in physical-mechanical properties. We developed a method for fabricating laminated samples from thin films prepared by spin casting the polymer from dilute solutions. The samples prepared in this manner show no significant change in molecular weight. The choice of solvent, however, does affect the mechanical properties of the laminated samples; poorer solvents afford samples with better flexural strength and modulus.

The lamination technique was easily adapted to the addition of reinforcing materials to the poly lactide films. The incorporation of high-modulus carbon fibers results in improved flexural strength and modulus values essentially equivalent to those of

Table VI. Orientation of Poly(DL-lactide)

<u>Sample</u>	<u>Flexural Strength</u> <u>X 10<sup>3</sup> psi</u>	<u>Flexural Modulus</u> <u>X 10<sup>6</sup> psi</u>
PLA unoriented	5.8	0.27
PLA oriented	4.9	1.06

bone. These composite materials offer considerable promise as implants in maxillofacial surgery.

Our latest research efforts show that orientation of polylactide samples by stretching them at the glass-transition temperature increases the flexural modulus values by about 400% over the control values. These materials with increased flexural modulus are much stiffer (similar to bone) and will probably have less tendency to warp or distort when implanted in the body.

Both the lamination technique with incorporation of reinforcing fibers and sample orientation provide biodegradable polylactide materials with significant improvements in flexural properties. Further research and optimization studies on these approaches should give biodegradable materials acceptable for maxillofacial implantation.

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